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REPLY BRIEF

Attorney Docket No. 30775-701.403

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re the Application of: Applicant: Jonathan W. Nyce Serial No.: 10/072,010 Filed: October 25, 2001 Title: Compositions For Treatment Of Asthma Or Bronchoconstriction	Confirmation No.: 5176 Group Art Unit: 1617 Examiner: San Ming R. Hui Customer No. 021971
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APPELLANTS' REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

MAIL STOP APPEAL BRIEF - PATENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants submit this reply brief in accordance with the provisions of 37 C.F.R. § 41.41 in response to the Examiner's Answer mailed April 4, 2007.

I. STATUS OF CLAIMS

The application under appeal currently includes claims 160-162, 165, and 187-190. Claims 160-162 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast U.S. Patent 4,956,355 (Prendergast), in view of Lieberman et al., "Pharmaceutical Dosage Forms", page 110, (Lieberman) and Gennaro, Alfonso R., "Remington: The Science and Practice of Pharmacy", 17th Ed., 1985, page 1505 (Remington).

Claims 187-189 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Prendergast, Lieberman and Remington as applied to claims 160-162, 165 above, and further in view of Kelly et al., "Chapter 24/Asthma", 2nd Ed., 1992, pages 408-449 (Kelly).

Claims 160-162, 165 and 187-190 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce U.S. Patent 5,527,789 (Nyce) in view of Lieberman., Remington, and Kelly. Claims 160-162, 165, and 187-190 are appealed.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellant respectfully requests the Board of Patent Appeals and Interferences to review the following grounds of rejection on appeal:

1. Whether claims 160-162 are patentable under 35 U.S.C. 103(a) Prendergast in view of Lieberman and Remington.
2. Whether claims 187-189 are patentable under 35 U.S.C. 103(a) over Prendergast, Lieberman, and Remington, further in view of Kelly.
3. Whether claims 160-162, 165 and 187-190 are patentable under 35 U.S.C. 103(a) over Nyce in view of Lieberman, Remington, and Kelly.

III. ARGUMENT

This Reply Brief responds to arguments raised by the Examiner in the Examiner's Answer.

Rejection of Claims 160-162 Under 35 U.S.C. §103(a) Over Prendergast in view of Lieberman and Remington

I. The Examiner improperly uses the Ansel and Remington 20th Edition references, which were not included in the Examiner's grounds of rejection

In the Examiner's Answer, the Examiner states that "the secondary references, i.e., Remington and Ansel, both well accepted text references, teach that the optimal particle size for inhalation is 0.5-7 μ m or 0.5-5 μ m." In the Office Actions, the Examiner cited both the 17th and the 20th Edition of Remington. It is improper for the Examiner to use Ansel or Remington 20th Edition: First, because neither reference is included under the grounds of rejection by the Examiner, and second, because Remington 20th Edition, published in 2000, was published five (5) years after the February 24, 1995 priority date of this application. These references are not included as grounds of rejection by the Examiner, but are relied upon as part of the argument for rejection. These references were not used by the Examiner simply to assert a universal fact, but were used as a substantive part of the Examiner's rejection in this Appeal in the Examiner's Answer. Where a reference is relied on to support a rejection, whether or not in a minor capacity, that reference should be positively included in the statement of the rejection. See *In re Hoch*, 428 F.2d 1341, 1342 n.3 166 USPQ 406, 407 n. 3 (CCPA 1970). The use of these references during prosecution, and the continued reliance of the Examiner on these references, is improper. Thus the obviousness rejection under §103 is improper and should be reversed.

II. The Examiner is incorrect in rejecting Appellant's arguments by stating that "the intended use of how to use the powder composition are considered moot"

In the Appeal Brief, Appellant asserts that the Examiner has not established a motivation to combine the teachings of the textbooks, Lieberman and Remington, with Prendergast, which teaches the use of DHEA to treat HIV. The Examiner attempts to reject Appellant's arguments because the

claims are directed to a composition, stating: “the issue at hand is not how the composition will be effected in the body” (Examiner’s Answer page 10) and “the intended use of how to use the powder composition are considered moot” (Examiner’s Answer page 11). Then the Examiner takes the opposite position to reject the claims specifically based on how the DHEA compounds are administered. It is improper and inconsistent for the Examiner to sweep away Appellant’s rebuttals of those arguments simply by stating that because the claims are directed to compositions, the point is moot. Thus, the Appellant has made legitimate arguments in the Appeal Brief directed at rebutting the Examiner’s assertion that it would have been obvious to combine specific sections of pharmaceutical textbooks with a patent on treating HIV with DHEA. Appellant’s arguments should not be disregarded by the Board as the Examiner suggests, just because the claims are directed toward a composition. The intended use of the claimed composition is relevant for the invention taken as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 U.S.P.Q. 43, (C.C.P.A 1963).

Appellant notes that after the Examiners Answer, the Supreme Court decided *KSR Int’l. Co.v. Teleflex, Inc.* No. 04-1350, (April 30, 2007) (“*KSR*”) which affects the interpretation of the law, see *In re Papeset*??? (CITE) with respect to the determination of obviousness under 35 U.S.C. 103(a). Appellant believes that the arguments submitted in the Appeal Brief relating to the non-obviousness of the claims at issue still stand in light of *KSR*. In particular, while *KSR* warns against the rigid application of the teaching, suggestion, motivation test, the test itself has not been rejected. The Court noted that the analysis under 35 U.S.C. 103(a) “should be made explicit” (*KSR*, slip op. at 5) and that it is “important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does” (*Id.* at 14). This interpretation of *KSR* is consistent with the guidance from the U.S. Patent Office (see attached copy of Memorandum from Deputy Commissioner of Patents to the Technology Center Directors dated May 3, 2007). For the reasons described above and in the Appeal Brief, the Examiner has failed to explicitly identify a reason that would have prompted a person of ordinary skill in the art to combine the elements. Thus, the obviousness rejection under §103 should be reversed.

III. The Examiner mischaracterizes Appellant's use of Table 1 of Remington listing modes of drug delivery and medicinal and pharmaceutical agents

In the Appeal Brief, Appellant includes Table 1, which provides listing modes of drug delivery and medicinal and pharmaceutical agents from Remington 17th Edition, a reference cited by the Examiner. In the Examiner's Answer, the Examiner states that the citing of Table 1 by Appellant was misplaced (Examiner's Answer page 11). Table 1, however, was cited by Appellant rebut the Examiner's argument the claims are shown to be obvious by putting together the pieces: DHEA can be used to treat patients for HIV, drugs can be administered by inhalation, and a particle size range of 1-5 μm can be advantageous. The Examiner, with hindsight, was able to refer back to textbooks and find all of the pieces. However, if one views the teachings in the literature in context, as a whole, as seen by one skilled in the art at the time, it does not appear obvious to put all of the disparate pieces together. Table 1 demonstrates the large number of potential modes of administration and the vast number of drugs known at the time of the invention, leading to a very large number of combinations. This large number of possibilities refutes the Examiner's contention that one of ordinary skill in the art would be motivated to combine a specific couple of pages in Remington with a specific couple of pages of Lieberman with a teaching by Prendergast to use DHEA to treat HIV.

It is improper for the Examiner to pick and choose only those parts of a reference to support his position when a number of other combinations are equally feasible. See, *Ex parte Fleishmann*, 157 USPQ 155; *Ex parte Garvey*, 41 USPQ 583 (1939). As properly held in *In re Wesslaw*, 147 USPQ 391, 393 (CCPA 1968), "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." Hence, the Examiner has done a "pick and choose" of only that part of Remington to support his position and attempts to disregard the parts that would not support the rejection.

IV. The Examiner mischaracterizes Appellant's reference to parts of Lieberman not explicitly cited by the Examiner

Appellant asserts in the Appeal Brief that the Examiner chose portions of Lieberman to support his argument that DHEA in the claimed particle size range is obvious, but that Lieberman, taken as a whole, does not support this argument. Appellant cited *Hartness v. Simplimatic Eng'g*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1832 (Fed.Cir.1987) for the proposition that the prior art as a whole must make the invention obvious. To support this argument, Appellant referred to a section of Lieberman (pages 32-27) not specifically cited by the Examiner, that does not teach making the claimed particle size range, and if anything teaches away from the use of particles that are too small, warning against going below a "critical size". (Attached are copies of the relevant pages which Appellants believe were sent with the Appeal Brief, but Examiner states were missing). In the Examiner's Answer, the Examiner attempts to rebut this argument by saying "one cannot apply piecemeal analysis to attack the references individually". First, this is one of a number of examples of the Examiner improperly stating rules without providing support for them. Second, the Appellant's reference to this portion of Lieberman is the opposite of a piecemeal analysis. The Appellant's point is that Lieberman, as a whole, does not support the argument that a particular particle size range of DHEA is obvious, and that that taken as a whole, Lieberman teaches that there are important, compound-specific properties such as the "molecular composition and arrangement" that must be considered when deciding what particle size will be used for making a pharmaceutical formulation of a drug.

V. The Examiner improperly cites "general textbook teachings" in the Examiner's Answer to rebut unexpected results.

In the Appeal Brief, Appellant asserts that during prosecution, the Examiner did not address the unexpected results submitted by the Appellant; failing to address the substance of the results, and rejecting them with a simple statement that there was no "side by side" comparison with the prior art (again invoking a test that the Appellant has to meet without providing any support for requiring it). Appellant cited *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995), which

holds that the Examiner has the burden of specifically addressing the substance of unexpected results identified by the patent applicant during prosecution. In order to rebut these arguments in the Appeal Brief, the Examiner attempts in the Examiner's Answer for the first time to specifically address these results. It is improper for the Examiner to present new substantive arguments here. In the Examiner's Answer, the Examiner cites, for the first time, "general textbook teachings" (Examiner's Answer page 13), that "one of ordinary skill in the art is charged to have in his possession", and from which "it would be clear that the so-called unexpected results are not unexpected". This line of argument by the Examiner, even if it was made during prosecution, is improper. By citing "general textbook teachings" followed by a conclusory statement of obviousness, the Examiner does not explicitly identify a reason that would have prompted a person of ordinary skill in the art to combine the elements, a responsibility that was affirmed in *KSR* (*KSR*, *Id.* at 5 and 14). Thus, the Examiner's statements in the Examiner's Answer support Appellant assertions in the Appeal Brief that the Examiner has failed to address the unexpected results presented by Appellant during prosecution.

Rejection of Claims 187-189 Under 35 U.S.C. 103(a) Over Prendergast, Lieberman, and Remington, further in view of Kelly

VI. The Examiner mischaracterizes Appellant's arguments that these references which teach only a 1-5µm particle size should not be used to reject a claim to a 15-500µm particle size range

The present patent application has one set of claims (160-162, 165) directed to a pharmaceutical composition comprising particles in the 1-5µm size range, and another set of claims (187-189) directed to a pharmaceutical composition comprising particles in the 15-500µm size range. With respect to the first set of claims, as described above, the Examiner argues that Prendergast, Remington, and Lieberman combined render obvious a pharmaceutical composition of DHEA in a particle size range of 1-5µm. Part of the argument is that Remington teaches a particle size range of 0.5-7µm. The Examiner then uses same three references, to support an obviousness rejection of the claims to a particle size range of 15-500µm. Appellant asserts in the Appeal Brief that it is not correct for the Examiner to reject claims to a particle size range of 15-500µm using a

teaching from Remington to a particle size range of 0.5-7 μ m. These particle size ranges are patentably distinct from one another, and there is nothing in the prior art cited by the Examiner to teach them as obvious over one another much less obvious over the prior art. The Examiner's use of the references in this manner support the contention described above that the Examiner is picking and choosing the parts of references that support the rejection, as prohibited by *Wesslaw, Id.* at 393, and is not considering the teaching of the art as a whole.

Thus, for the reasons described above, the Examiner has not presented a prima facie case for obviousness. Therefore, the rejection based on obviousness is in error, and the rejection should be reversed.

CONCLUSION

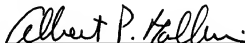
For the reasons stated above, claims 160-162, 165, and 187-190 are patentable over the prior art of record, and the rejections to those claims under 35 U.S.C. § 103 are improper and should be withdrawn. Appellant respectfully requests the Board to reverse the Examiner's rejections with instructions to allow the claims.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 30775-701.403).

Respectfully submitted,

Date: May 31, 2007

By:



Albert P. Halluin (Reg. No. 25,227)
Robert H. Reamey (Reg. No. 50,371)

WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304-1050
Telephone No. (650) 493-9300
Facsimile No. (650) 493-6811

ATTACHMENTS

- 1) Memorandum from Deputy Commissioner of Patents to the Technology Center Directors dated May 3, 2007
- 2) Lieberman et al., "Pharmaceutical Dosage Forms", pages 32-37.



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1480
ALEXANDRIA, VA 22313-1480
www.uspto.gov

MEMORANDUM

DATE: May 3, 2007

TO: Technology Center Directors

FROM: Margaret A. Focarino
Deputy Commissioner
for Patent Operations

SUBJECT: Supreme Court decision on *KSR Int'l. Co., v. Teleflex, Inc.*

The Supreme Court has issued its opinion in *KSR*, regarding the issue of obviousness under 35 U.S.C. § 103(a) when the claim recites a combination of elements of the prior art. *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007). A copy of the decision is available at <http://www.supremecourt.us/opinions/06pdf/04-1350.pdf>. The Office is studying the opinion and will issue guidance to the patent examining corps in view of the *KSR* decision in the near future. Until the guidance is issued, the following points should be noted:

- (1) The Court reaffirmed the *Graham* factors in the determination of obviousness under 35 U.S.C. § 103(a). The four factual inquiries under *Graham* are:
- (a) determining the scope and contents of the prior art;
 - (b) ascertaining the differences between the prior art and the claims in issue;
 - (c) resolving the level of ordinary skill in the pertinent art; and
 - (d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

- (2) The Court did not totally reject the use of “teaching, suggestion, or motivation” as a factor in the obviousness analysis. Rather, the Court recognized that a showing of “teaching, suggestion, or motivation” to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

- (3) The Court rejected a rigid application of the “teaching, suggestion, or motivation” (TSM) test, which required a showing of some teaching, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the prior art elements in the manner claimed in the application or patent before holding the claimed subject matter to be obvious.

(4) The Court noted that the analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it was "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. The Court specifically stated:

Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an **apparent reason** to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis **should be made explicit**.

KSR, slip op. at 14 (emphasis added).

Therefore, in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

PHARMACEUTICAL DOSAGE FORMS

Tablets

SECOND EDITION, REVISED AND EXPANDED

In Three Volumes

VOLUME 2

EDITED BY

Herbert A. Lieberman

H. H. Lieberman Associates, Inc.
Consultant Services
Livingston, New Jersey

Leon Lachman

Lachman Consultant Services
Westbury, New York

Joseph B. Schwartz

Philadelphia College of Pharmacy and Science
Philadelphia, Pennsylvania

MARCEL DEKKER, INC.

New York and Basel

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population being samples in the enclosure (drum, mixer, storage hopper, etc.).

Probably the most significant measure of quality of a mixture is how the blend actually performs, and the uniformity of the final product. However, Current Good Manufacturing Practice (CGMP) Regulations require documentation of a controlled process at each step of manufacturing.

V. MATERIAL PROPERTIES: BASIC CONCEPTS OF DRY BLENDING—THE UNIT PARTICLE

Since mixing plays such an important role in tableting, an understanding of the characteristics of the materials being mixed is paramount. Many of the studies presented in the literature, and used previously in examples, deal with binary mixtures of physically and chemically similar materials which can easily be differentiated for the study by color, size, or assay. However, pharmaceutical, binary, particulate systems in tableting are the exception, and results dealing with binary systems have limited applicability in industrial practice.

Each component in a mixture has distinct physical characteristics which contribute to, or detract from, the completeness (uniformity) of a mixture. Therefore, it is important to define and characterize the unit particles that make up the mixture, whether it is a premix of a wet granulation, a direct compression formula, or the addition of lubricants, etc., to a granulation. Figure 21 is an illustration of several different types of particles handled in tablet granulation mixing.

The unit particles in a system may range from the less-than-1 μ m-size pure substance raw material particle to the 8 to 12 mesh multicomponent granule held together by a binder. Since dry mixing is a dynamic state of an assemblage of particles, the properties of the unit particle must be discussed in terms affecting these dynamics.

There are three properties intrinsic to each component in the mixture: "composition (physicochemical structure), size (and size distribution), and shape" [31].

Composition of each particle is "its qualitative and quantitative makeup" [32]. Each unit of pure substance has its own molecular composition and arrangement that distinguishes it from all other materials, and dictates its behavior in part as a powder per se, or in combination with other tablet mixture ingredients. Chemical composition is important, because chemical reactivity limits a material's use with other tableting components, e.g., acids and bases such as aspirin and phenylpropanolamine would not be blended together because of their potential to react. The same applies to components that may affect the stability of a mixture such as the potential Schiff Base reaction between certain sugars and amines when in contact even in the dry state.

Physically, the molecular makeup determines crystallinity manifested as color, hardness, tackiness, general appearance, etc.

Particle size and size distribution of the unit particles have considerable impact on the flow properties of powders and therefore, the dynamics of mixing. Table 5 shows, in general, the effect of particle size on the flow properties of powders. Table 6 is a list of some common substances used in the pharmaceutical industry, and their flow characteristics. A very complete and detailed list of materials and their characteristics

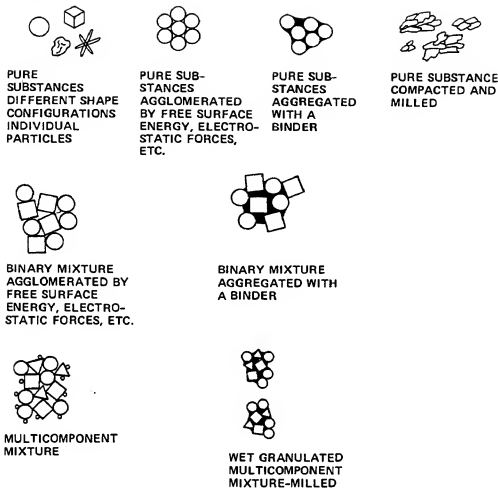


Figure 21 Several different types of particles encountered in tablet granulation dry blending.

may be found in the reference text: *Handbook of Pharmaceutical Excipients* [33].

Large (sieve size range >60 mesh) dry particles have a tendency to flow better than the smaller dry particles, because they have greater mass. Smaller particles (<100 mesh) may create mixing problems because surface areas are very great, and may give rise to strong electrostatic forces as a result of processing and/or inter-particle friction from movement. These forces may prevent the desired distribution of these smaller particles throughout a mixture because of fine particle agglomeration.

As the particle size approaches 10 μm and below, weak polarizing electrical forces called van der Waals forces or cohesive forces also begin to affect the flow of the powder. Both van der Waals and electrostatic forces usually inhibit powder flow through particle agglomeration as mentioned above. However, in some instances improved flow results because

Table 5 Effect of Particle Size on Powder Flow

Particle size	Type of flow ^a	Reason
200–250 μm (10–60 ^b mesh)	Flow is usually good if shape is not interfering	Mass of individual particles is relatively large
250–75 μm (60 mesh–200 μm)	Flow properties may be a problem with many pure substances and mixtures	Mass of individual particles is small and increased surface area amplifies effects of surface forces
<100–75 μm	Flow becomes a problem with most substances	Cohesive forces or free surface energy forces are large as well as static electrical forces relative to particle size

^a Assume particle shape is constant and does not interfere with flow.

^b U.S. standard mesh size.

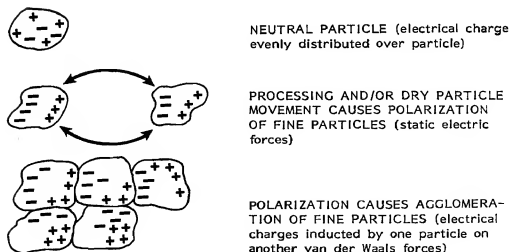


Figure 22 Effect of electrical forces on fine particles.

the agglomerated particles behave as a single large mass particle (Fig. 22). Flow may be better in this case, but the dynamics of distributing these small particles during mixing is very poor.

Increased surface exposure of fine particles to the atmosphere may present oxidation and/or moisture adsorption/absorption problems which should be avoided if possible. Fine powder particles also create potential dust conditions which may require operators to wear respirators for safe handling, and may also create potentially dangerous dust explosion hazards.

Particle size distribution of unit particles as suggested in the above discussion may also have an effect on the flow of a powder, i.e., too large a percentage of fine particles with cohesive forces, or free surface energy may inhibit flow. Although it has been stated that cohesive forces are strong in powders composed of particles 10 μm or less in size, each powder has a "critical size" where cohesive forces begin to affect the powder flow properties. An example of this is shown in Table 7.

The "angle of repose" (α) or the "angle of slip" is a relative measure of the friction between powder particles but also is a measure, for the most part, of the cohesiveness of fine particles. The angle of repose may be measured in several ways as shown in Figure 23. Methods 1 and 2 are both dynamic angle of repose measurements: the powder in Method 1 flows from a filled powder funnel onto a smooth surface where the angle is measured as illustrated, and in Method 2 the powder is moving in a rotating drum while the angle is measured as shown. Method 3 gives the static angle of repose, because the powder container is removed and the powder does not, or is not flowing before the measurement.

Since many factors enter into the angle of repose such as particle size, shape, moisture content, etc., there is some question as to its value in characterizing a powder. However, certain generalizations can be made regarding the angle of repose:

1. α is $>60^\circ$ for cohesive powders.
2. α is $<25^\circ$ for non-cohesive particles.
3. High (α) usually means poor powder flow and the particles are usually less than 75 to 100 μm in size.
4. Low (α) usually mean good powder flow and the particles are usually greater than 60 mesh or 250 μm in size.

The tangent of the angle repose ($\tan \alpha$) is termed the "coefficient of friction" of a powder and is preferred by some in referring to the flow properties of a powder. For example, a powder with an angle of repose of 65° will have a coefficient of friction of

$$\tan 65^\circ = 2.14$$

Whereas, a powder with an angle of repose of 35° will have a coefficient of friction of

$$\tan 35^\circ = 0.700$$

Table 6 Flow Characteristics of Some Common Substances

Material	Working bulk		General comments on flow
	density (gm/cm ³)	Type of powder	
Aerowax C	0.46	Very fluid powder	Dusty, slippery material
Ammonium chloride	0.75	Nonuniform powdered granules	May form hard lumps, as a result of hygroscopicity
Calcium carbonate	0.92	Fluid cohesive powder	Flow becomes very poor if powder is packed
di-Calcium phosphate	0.96	Cohesive powder	
	0.99	Uniform granules	Powder form is very dusty. Material is hygroscopic which reduces flowability
Cellulose	1.31	Very fluid granules and powder	
		Fibrous not free flowing and crystalline free flowing	Flow depends on size of fibers or crystals
Kaolin	0.48	Fluid powder	Dusty material which has poor flow when powder is packed excessively

Magnesium hydroxide	0.56	Fluid powder	Dusty material which is hygroscopic. Flowability is reduced considerably when powder is packed excessively
Sodium chloride	1.10	Uniform granule or fluid granules and powder	Material is very hygroscopic and cakes at relative humidity: 40-50% at room temperature
Sodium bicarbonate	0.96 1.08	Fluid cohesive powder Uniform powdered granules	Very little dustiness. Material is hygroscopic which decreases flowability
Corn starch	0.56	Very fluid powder	Very dusty. Material is hygroscopic which decreases flowability
Talc	0.67 0.19	Fluid powder Fluid cohesive powder	The two density powders are slippery and very dusty. Material is hygroscopic which decreases flowability
Titanium dioxide	0.56	Cohesive powder	Flow becomes extremely poor if packed
Zinc oxide	0.45 0.74	Fluid cohesive powder Cohesive powder	Dusty, tends to lump. Flow becomes poor when packed. Some dustiness tends to lump. Flow becomes poorer when packed

Source: Cart, R. L., Jr., Chem. Eng., Feb., 1:69-72 (1965).